DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FILE COPY

April 7, 2000

David E. Moll, President & CEO
ILTC
3389 Sheridan Street, Suite 49
Hollywood, FL 33021

Dear Mr. Moll:

Your petition requesting the Food and Drug Administration to find benzalkonium chloride (0.11%-0.13%) is generally recognized as safe and effective as defined by the tentative final monograph for health-care antiseptic drug products was received by this office on 04/06/00. It was assigned docket number 75N-183H/CP 3 and it was filed on 04/06/00. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter in that it in no way reflects an agency decision on the substantive merits of the petition.

Sincerely,

Lyle D. Jaffe

Lyle D. Jaffe
Dockets Management Branch

75N-183H

ACK 1

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20859

00 APR -6 P3:13

April 6, 2000

Re: Citizen Petition to Request FDA Find Benzalkonium Chloride (0.11%-0.13%) is Generally Recognized as Safe and Effective as Defined by the Tentative Final Monograph for Health-Care Antiseptic Drug Products

Dear Sir or Madam:

CITIZEN PETITION

The undersigned submits this petition under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), Sections 502, 505 and 701(a), 21 U.S.C. §§ 352, 353, and 371(a), and 21 C.F.R. §§ 330.10, 333 and 369 to request that the Commissioner of Food and Drugs take the following actions:

A. Actions Requested

1. Consider this submission as a petition to amend the Tentative Final Monograph for topical antimicrobial drug products for over-the-counter (OTC) human use despite the lack of a final monograph because good cause warrants consideration.

2. Find benzalkonium chloride in a concentration of 0.11% to 0.13% is generally recognized as safe and effective and not misbranded for use as the active ingredient in an OTC antiseptic handwash and include it in the final monograph for topical antimicrobial drug products for OTC human use by adding it to the active ingredients listed in subpart E, § 333.410 of the Tentative Final monograph for Health-Care Antiseptic Drug Products.

B. Statement of Grounds

1. Consideration of this Petition

Information submitted after the expiration of the comment period on an OTC monograph is treated as a petition to amend the monograph. 21 C.F.R. § 330.10(a)(7)(v). The Commissioner may consider new information in a petition to amend a monograph prior to publication of the final monograph if "good cause has been shown that warrants earlier consideration." *Id.* The time period for

submitting comments to the Tentative Final Monograph for Health-Care Antiseptic Drug Products (the "Tentative Final Monograph"), 59 Fed. Reg. 31402 (June 17, 1994), has expired but the monograph is not yet finalized. Good cause warrants the consideration of the information in this petition.

Specifically, the undersigned, International Laboratory Technology, Corp. (ILTC), has developed a benzalkonium chloride preparation (concentration 0.11% - 0.13%) for use as an OTC antiseptic handwash that kills 98% of *staphylococcus aureus* ("staph") bacteria for up to four hours post use. The data supporting the safety and efficacy of this benzalkonium chloride preparation are detailed below and attached to this petition. A recent news report noted that according to Center for Disease control data, hospital-acquired infections (such as staph) will contribute to the deaths of 70,000 people in the United States. *See* Tab 1. ILTC's product could help reduce this outbreak. Accordingly, good cause warrants that this petition should be considered to amend the Tentative Final Monograph despite the lack of a final monograph.

2. Benzalkonium Chloride is Safe and Effective

a. Efficacy of Benzalkonium Chloride

The Agency has found benzalkonium chloride to be generally recognized as safe and effective in products for short-term use, such as first aid antiseptic drug products. *See* 59 Fed. Reg. at 31425; *see also* 56 Fed. Reg. 33644, 33663 (July 22, 1991). The Tentative Final Monograph lists benzalkonium chloride as a Category III ingredient for any other use. Based on the data submitted with this petition, ILTC requests that the Agency find that benzalkonium chloride is generally recognized as safe and effective for use as the active ingredient in an OTC antiseptic handwash. ILTC is submitting this petition at this time to begin the review process.

As suggested in the Tentative Final Monograph, 59 Fed. Reg. at 31437, ILTC communicated with the Agency to determine the data necessary to support a determination that benzalkonium chloride was generally recognized as safe and effective as an OTC antiseptic handwash. On September 22, 1999, as a result of those discussions, ILTC received the attached letter outlining a specific testing agenda for this product. *See* Tab 2. Specifically, this letter stated:

> . . . the following tests . . . will provide data necessary to support safety, efficacy and persistence claims, as well as support the inclusion of the ingredient benzalkonium chloride for use in the Tentative Final Monograph for Health-Care Antiseptic Drug Products dated June 17, 1994.

In vitro Tests

1. A time kill study conducted per the Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products dated June 17, 1994.
2. An MIC [Minimum Inhibitory Concentration] study using 50 strains of each organism listed in the monograph against the test product, 10 strains of each with the vehicle and a positive control (Hibiclens (chlorhexidine gluconate)).

In vivo Tests

1. Conduct a Healthcare antiseptic handwash study as outlined in the TFM. This study should include a total of 60 subjects, 30 treated with the test product and 30 treated with a reference product....
2. A Cylinder Sampling Test and an Agar Patch Test to demonstrate persistence.

See Tab 2.

ILTC has performed the time kill study, the Healthcare antiseptic handwash study and the Agar patch test. Benzalkonium chloride (concentration 0.11% - 0.13%) passed each test per the specifications set forth in the Tentative Final Monograph. ILTC is performing the MIC study; final results of this study are expected in approximately two months and will be submitted to the Agency upon completion. These data are attached at Tabs 3 - 7. In summary:

1. A time kill study showed that benzalkonium chloride (0.11% - 0.13%) killed 99.9% of gram positive organisms, gram negative organisms and yeast cells within 60 seconds. *See* Tab 3.

2. An MIC study using benzalkonium chloride (0.11% - 0.13%) as the test product is ongoing. The results to date are attached. These preliminary results show benzalkonium chloride effectively kills the required strains. Final results will be submitted as soon as completed. *See* Tab 4.

3. A healthcare antiseptic handwash study (60 subjects) that showed that benzalkonium chloride (0.11% - 0.13%) achieved a greater than three $\log_{10}$ reduction at one, three, seven, and ten washes. The reference product achieved a greater than two log reduction after the first wash and greater than a three log reduction after the tenth wash. *See* Tab 5.

4. An Agar Patch Test that showed that benzalkonium chloride (0.11% - 0.13%) achieved a total inhibition against staph for up to four hours post application. Benzalkonium chloride (0.11% - 0.13%)

also achieved statistically significant persistence against *E. Coli* for up to four hours post application. *See* Tab 6. A Cylinder Sampling Test demonstrated a significant persistent antimicrobial effect for benzalkonium chloride (0.11% - 0.13%) at all study time points. *See* Tab 7.

These data support the conclusion that benzalkonium chloride (0.11% - 0.13%) is effective for use as the active ingredient in an OTC antiseptic handwash.

b. Safety of Benzalkonium Chloride

Based on the standard set forth by the Agency, *see* 39 Fed. Reg. 33102, 33135 (September 13, 1974), published data and tests performed by ILTC show that benzalkonium chloride is safe for use as the active ingredient in an OTC antiseptic handwash.

A 1989 publication of the *American Journal of Toxicology* contains a "Final Report on the Safety Assessment of Benzalkonium Chloride." *See* Tab 8. Although published in 1989, this report was not available on the docket for the Tentative Final Monograph and hence does not appear to have been previously submitted to or considered by FDA. This report presents data from a number of toxicology and safety studies performed with benzalkonium chloride. The panel concludes from these data that benzalkonium chloride "is not a sensitizer to normal humans at concentrations of 0.1%" and hence it "can safely be used as an antimicrobial agent at concentrations of up to 0.1%."

In addition, ILTC performed a 24-hour skin irritation study where benzalkonium chloride (0.11% - 0.13%) was tested against Purell (62% ethyl alcohol), sodium lauryl sulfate and physiological saline. Benzalkonium chloride resulted in less inflammation than sodium lauryl sulfate and Purell in the occlusive stage and had identical results to physiological saline. In the semi-occlusive stage, benzalkonium chloride resulted in less inflammation than sodium laurel sulfate and had the same results as Purell and physiological saline. *See* Tab 9.

Finally, the Environmental Protection Agency has registered benzalkonium chloride (USEPA PC code 069106) as an active ingredient in pesticides in concentrations much higher than 0.13%. Of the EPA-registered products that contain benzalkonium chloride, the one with the lowest concentration contains the active ingredient at 3.0% by weight. An EPA-registered product, if used in accordance with the labeled directions, is not expected to present "unreasonable risks" to human health or to the environment. This information further supports a finding that benzalkonium chloride is generally recognized as safe.

Taken as a whole, these data show that benzalkonium chloride in the concentration used by ILTC can be generally recognized as safe for use as the active ingredient in an OTC antimicrobial handwash.

3. Conclusion

Based on the data from ILTC's testing, FDA should find that benzalkonium chloride is generally recognized as safe and effective for use as the active ingredient in an OTC antimicrobial handwash. If the Agency requires any additional data, or would like to discuss the data submitted, please feel free to contact us. ILTC will endeavor to submit any additional data required by the Agency expeditiously.

C. Environmental Impact

Pursuant to FDA regulations, action on an OTC monograph that does not increase the use of the active moiety, or if it increases use of the active moiety the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion, are categorically excluded from an environmental impact assessment. 21 C.F.R. 25.31(a)-(b). Thus, no environmental assessment is required.

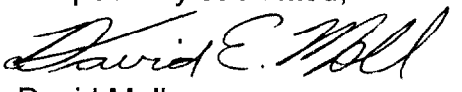
D. Economic Impact

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which petitioner relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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Thursday, April 06, 2000

Lyle Jaffe
FDA
FDA-Dockets Management Branch
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

Dear Mr. Jaffe:

It was a pleasure speaking with you today. As per our conversation, I am sending you this letter as written confirmation of our discussion. ILTC hereby authorizes the FDA to release any documents that are contained in our Citizen Petition seeking Category I inclusion for our antibacterial handwash containing Benzalkonium Chloride as an active ingredient. If pages in any of our studies are marked "Confidential", we hereby authorize the agency to release that data as well.

Thank you for addressing this issue so promptly. If I may be of any further assistance, please do not hesitate to call me.

Sincerely,

David E. Moll

David Moll
President & CEO